

c.) Remarks

The claims have been amended in order to recite the present invention with the specificity required by statute. Additionally, new claims 42-52 are presented in order to more specifically recite various preferred embodiments of the present invention. No new matter has been added.

The Examiner has objected to the abstract for the formal reasons noted. In response, the abstract has been amended to address the issues raised by the Examiner.

Claim 38 is also objected to because Applicant is required to spell out "GSK-3" at the first usage. The basis for this objection is unclear since the term "GSK-3" is plainly defined in the specification. Nonetheless, solely in order to reduce the issues, claim 38 has been cancelled and independent claims 4, 5, 11 and 16 have each been amended to spell out "GSK-3". New independent claims 42, 47, 49 and 50 are written similarly.

Claim 38 is rejected under 35 U.S.C. §112, first paragraph, because the Examiner states only enhancing neurogenesis of Tuj1 positive neurons and reversing the suppression effect of A β on neurogenesis by lithium chloride, kenpaullone, SB-216763, indirubin-3'-monoxime or siRNA to inhibit expression of GSK-3 β is enabled. Although this rejection is respectfully traversed, the independent claims are above amended to recite these relevant features, in order to expedite prosecution.

Claim 38 is also rejected under 35 U.S.C. §112, first paragraph (as containing subject matter which was not described so as to reasonably convey the inventors had possession of the claimed invention) and second paragraph (as being

indefinite for failing to particularly point out and distinctly claim the present invention).

These rejections, too, are overcome by the foregoing amendment.

Claim 38 is rejected under 35 U.S.C. §102(b) as anticipated by WO 03/004485 (PCT/JP02/06776). Claim 38 is also rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,040,180 in view of Chen et al. (*J. Neurochem.*, Vol. 75 (2000), 1729-34) and Cross et al. (*J. Neurochem.*, Vol. 77 (2001), 94-102). Although claim 38 is cancelled, Applicants wish to address the cited art *vis a vis* the pending claims.

As to WO 03/004485, such was not published until January 16, 2003 so it is not available as under 35 U.S.C. §102(b). Moreover since it was not filed in English, it is also not entitled to its April 7, 2002 PCT filing date.

In support of the rejection, the Examiner states that page 153 of U.S. 2004/0167171 (a U.S. family patent of WO 03/004485) teaches a method of enhancing neurogenesis in a neural cell cultures in the presence of a substance that inhibits the activity of GSK-3 β . The Examiner specifically states that '171 teaches several inhibitors of GSK-3 β including SB-216763 (see p. 42, 1st column, line 39) and a method of enhancing neuronal differentiation from cells isolated from 2 day old rat cerebral cortex in a culture medium in the presence of an inhibitor of GSK-3 β (see p. 153).

As the Examiner appreciates, a salient feature of the present invention lies in Applicants' finding that GSK-3 inhibitors promote neurogenesis. Respectfully submitted, the Examiner's understanding of the '171 publication is incorrect.

The '171 publication teaches neither (i) any compounds recognized to have GSK-3 β inhibitor activity, nor (ii) that such inhibitors are useful in promoting neurogenesis.

The '171 publication teaches that novel compounds (described as compound (I) (see p. 12, [0136])) are useful as active agents for promoting a proliferation/differentiation of neural stem cells and/or neural precursor cells for transplantation¹ (see claim 40). However, all structures of the compounds recited in Applicants' claims differ in kind from those of compound (I) in the '171 publication.

The '171 publication also teaches that, in addition to the active agent of compound (I), other ingredients (among which SB-216763 is exemplified) may be used together therewith (see p. 41 [0568]). SB-216763 is a 3-aryl-4-indolylmaleimide derivative (namely 3-(2,4-dichlorophenyl)-4-(1-methylindole-3-yl)-1H-purrole-2,5-dione) having a nucleus skeleton of formula (II).

However, there is no teaching or suggestion that SB-216763 is (i) a GSK-3 inhibitor or (ii) use of SB-216763 as an active agent to promote neurogenesis.

As to the rejection over Chen and Cross, Chen teaches that lithium can enhance neurogenesis in the adult rodent hippocampus because lithium produced a 25% increase in the BrdU-labeled cells in the dentate gyrus (Abstract).

However, those of ordinary skill in the art appreciate that BrdU is not a marker for cell division, but rather a marker for DNA synthesis (see Rakic, *J. Neurosci.*, Vol. 22, No 3 (2002), 614-618, copy attached to the accompanying Information Disclosure

¹ The 2004/0167171 publication discloses a method of using compound (I) to enhance neuronal differentiation from cells isolated from 2 day old rat cerebral cortex in a culture medium optionally with 'SB-216763' (see p. 153 [1256]-[1257]).

Statement). Thus, increase in BrdU uptake does not mean neurogenesis is inherently increased. For example, BrdU-labeled cells can increase when repair of injured neuron cells is enhanced without neurogenesis. This deficiency is not addressed by Cross.

Cross simply suggests that SB-415286 and SB-216763 are inhibitors of GSK-3 β and can be used to protect neuronal cell death. However, to “protect neuronal cell death” is very different from enhancing neuronal differentiation from neural stem cells. Accordingly, the subject matter of the pending claims is neither anticipated nor obvious over these references, whether taken singly or in combination.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 4-19 and 42-52 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

/Lawrence S. Perry/
Lawrence S. Perry
Attorney for Applicants
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

LSP\ac

FCBS_WS 1418212_1.DOC